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(57) Abstract

A multiphase pharmaceutical composition for the topical treatment of a skin or anorectal condition, which includes an aqueous phase containing one or more medicaments for treating said condition, an oil phase containing a silicone oil, and porous particles also containing a silicone oil and adapted for delayed release of the silicone oil, whereby application of the composition to an affected region deposits said medicament(s) thereon and a protecting layer of silicone oil is formed over the medicament(s). Suppositories containing a silicone oil both in free form and in porous particles for slow release are also described.

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COMPOSITIONS FOR THE TREATMENT OF SKIN AND ANORECTAL CONDITIONS

This invention concerns pharmaceutical compositions and especially creams for the treatment of skin and anorectal conditions.

Such conditions often require the frequent application of medicaments and the site of application is normally left uncovered. There is however a tendency for the medicament to be removed for example by moisture, particularly in anorectal conditions such as haemorrhoids and anal fissures which are usually treated with combinations of astringents, antiseptics, topical analgesics, vasoconstrictors, antispasmodics and anti-inflammatory steroids. The healing of the lesions can also be inhibited by the mucous environment which, for example, leads to maceration of moist perianal skin.

The application of medicaments in an occlusive layer which repels water from the treated area can be ineffective as such conditions tend also to cause retention of fluids produced by the tissues. An occlusive layer can thus itself cause maceration of the affected area, which exacerbates the problem. It is also difficult to ensure that the occlusive layer does not form a barrier which prevents the medicaments from reaching the intended site of application.

US 5422117 (EP-A-0486117) and WO 90/07324 describe multiphase compositions having at least one phase containing medicaments and another phase for delayed release of a silicone oil. The silicone oil may be included in porous particles or microcapsules so that in use the composition deposits medicaments on the affected region and a layer of silicone oil is formed thereover, so protecting the medicaments from erosion by aqueous media while allowing water vapour to pass through the protective layer.

We have now found that the protective effect of the silicone oil can be improved by additionally including it in an oil phase as well as in porous particles. The silicone oil in the oil phase reduces the diffusion of the silicone oil from the porous particles, thus providing a longer lasting protective film, and can also provide a rapid protective effect. The invention is also concerned with oil phases which are specifically designed to function in this way.

We have also found that the inclusion of a gelling agent in the aqueous phase can also prolong the release of the silicone oil from the porous particles, by forming an emulsion barrier around the droplets of the oil phase and thus retarding the diffusion of the silicone oil from the porous particles into the oil phase.

It has also been found that the therapeutic effect of the compositions can be enhanced by optimising the solubility of the active ingredients in the aqueous or the oil phase, for example by the use of a cosolvent or coupler. Further, the effectiveness of the compositions can be improved by providing for delayed release of the active ingredients from porous particles in addition to the rapid or immediate effect of the active ingredients in the aqueous phase or the oil phase.

The invention thus provides a multiphase pharmaceutical composition for the topical treatment of a skin or anorectal condition, which includes an aqueous phase containing one or more medicaments for treating said condition, an oil phase containing a silicone oil, and porous particles also containing a silicone oil and adapted for delayed release of the silicone oil, whereby application of the composition to an affected region deposits said medicament(s) thereon and a protecting layer of silicone oil is formed over the medicament(s).

The compositions are preferably formulated as creams.

The compositions are particularly suitable for the treatment of haemorrhoids and skin conditions such as eczema, dermatitis, dry skin, chapped skin, napkin rash, pruritus (pruritus ani, pruritus vulvae, senile pruritus), mild burns such as sunburn, hyperkeratosis, as an emollient, neurodermatitis, dermatoses, psoriasis, seborrhoeic dermatitis, lichenification, insect bites, intertrigo or leg ulcers. Active ingredients for the treatment of such conditions are included in the aqueous phase where they are soluble, and they can also be included in delayed release form as dry ingredients. Insoluble active ingredients can also be included as dry solid-phase ingredients.

The active ingredients which are included in the aqueous phase may be for example local anaesthetics, anti-inflammatory steroids, antibacterials, emollients or astringents such as bismuth gallate. The compositions are particularly suitable for the formulation of local anaesthetics, such as benzocaine or lidocaine or salts thereof such as hydrochlorides, and steroids such as hydrocortisone or its acetate. Local anaesthetics may be present in a total amount of 0.1-10%, preferably 1-5% by weight, and anti-inflammatory steroids in an amount of 0.1-5% by weight.

Some of these active ingredients are poorly soluble in water and thus is especially so for anti-inflammatory steroids such as hydrocortisone and its derivatives. The compositions therefore preferably contains a cosolvent which act as a solubiliser for the active ingredients which are insoluble or poorly soluble in water and couples with them and carries them into water. The cosolvent is preferably N-methyl-2-pyrrolidone, for example in an amount of 1-5% by weight. This cosolvent is particularly useful with hydrocortisone as this can usually only be included as a suspension in creams and ointments when a large amount of alcohol is present. The solubilisation of the hydrocortisone, and also a

local anaesthetic in free base form, in this way can result in more effective penetration and faster action.

A co-solvent such as N-methyl-2-pyrrolidone can also be used in conjunction with another solvent such as a polyol (e.g. propylene glycol or ethoxydiglycol) or a polymeric solvent such as a polyoxypropylene/ polyoxyethylene copolymer (polaxamer) in order to enhance solubility and penetration. In general, no more solvent is used than is necessary to dissolve the ingredients.

The aqueous phase can also include a gelling agent. This increases the viscosity and physical stability of the composition, and also forms an emulsion barrier around the oil droplets present. This can protect the oil phase against diffusion of the silicone oil from the porous particles. The gelling agent may be a non-ionic or cationic hydrophilic gelling agent, preferably of a polymeric nature. Guar gum (a cationic gelling agent) or its derivatives may be used, but polyvinyl pyrrolidone and its derivatives (e.g. esters) are preferred. The gelling agent may be used in an amount of 1-5% by weight.

Bactericides such as benzalkonium chloride and chelating agents such as EDTA can also be included in the aqueous phase. The pH of the composition can be adjusted for example to 3.5-4.5 with acid, for example citric acid.

The oil phase of the compositions can be based on fatty acid esters, for example esters of straight or branched C_{12-22} (preferably C_{16-22}) fatty acids (such as stearic or isostearic acid) with alcohols, for example trihydroxy alcohols such as glycerol or diols such as propylene glycol. Mixtures of such esters may be used. The fatty acid esters are generally used in amounts of 5-25% by weight, preferably 10-15% by weight. Free fatty acids can also be included in the oil phase, for example C_{12-22}, preferably C_{16-18}, fatty acids such as

stearic acid, in a free unneutralised form. The acids can generally be used in amounts of 2-8%, preferably 4-6%, by weight.

The oil phase is preferably formulated to be relatively highly hydrophilic (i.e. made minimally lipophilic) to reduce or minimise the solubility of the silicone oil in this phase. This minimises the tendency of silicone oil to diffuse out of the porous particles and into the oil phase, thus giving a slower rate of release of silicone oil from the porous particles and hence a longer lasting protective effect. The lipophilicity of the oil phase can be reduced by the inclusion of high HLB emulsifiers such as polyoxyethylene derivatives of natural oils (e.g. PEG 40 hydrogenated castor oil) or of fatty alcohols (e.g. C_{12-22} alcohols such as cetyl, cetearyl, oleyl or stearyl alcohols), having HLB values of 8-17. The emulsifiers are preferably polyoxyethylene ethers of C_{16-22} fatty alcohols with HLB values of 14-17. Particular examples of such emulsifiers are laureth 3, 12 or 23, oleth 3, 5, 10, 20 and 25, ceteth 10, 20 and 25 and ceteareth 20. Cetyl and cetearyl alcohol ethers such as ceteth 25 and ceteareth 20 are preferred. The total amount of emulsifier(s) is generally within the range 1-5% by weight of the composition.

The silicone oil present in the oil phase, and also in the porous particles, is preferably a polydialkylsiloxane such as a polydimethylsiloxane oil or mixtures thereof. One such oil is Dimethicone Blend 200/350/1000 (Advanced Polymer Systems, Inc.), and in general any cosmetic or medical grade dimethicone with a viscosity of 100-1000 centistokes or blends thereof can be used. The total amount of silicone oil may for example be 7-15% by weight of the composition, with about 50-70% of this in the oil phase and 30-50% in the porous particles, by weight.

Silicone emulsifiers can also be included in the

oil phase to limit and control the emulsification of the silicone oil in the aqueous phase and its miscibility in the oil phase, and in turn to reduce or minimise the diffusion of the silicone oil from the porous particles. These emulsifiers can be based on polymethyl cyclosiloxanes, and an example is DC3225C (Dow Corning). They are preferably used in amounts less than necessary for complete emulsification of the silicone oil, e.g. up to 0.4% by weight.

The oil phase can also include an antioxidant such as butylated hydroxy toluene (BHT).

A wide range of porous particles are is known for carrying the silicone oil for delayed release, for example as described in WO 88/01164, WO 89/10132, US 4 873 091, US 4690825 and EP 306236A, the contents of which are incorporated herein by reference.

The porous particles may be composed of a wide range of materials. Many organic, synthetic polymers are suitable, as well as natural substances such as cellulose or gelatin. The choice of material will depend in part on the intended means of delayed release of the silicone oil, i.e. diffusion, compression, dissolving or melting.

The diameters of the particles will generally be in the range 1 to 1000 microns, preferably 5 to 100 microns, more preferably 10 to 25 microns. The surface area of the particles will generally range from about 1 to 500 m^2/g, preferably 20 to 200 m^2/g, and the total pore volume is preferably in the range 0.3 to 4.0 cm^3/g, more preferably 0.6 to 2.0 cm^3/g.

The porous particles preferably primarily release the silicone oil over a period of time by diffusion and also to some extent by the action of pressure to compress the particles. After the first application of the composition to the affected area, the use of gentle pressure, for example by rubbing, causes release of the silicone oil to provide a coating of oil over the layer

of cream. This initial effect is then followed by slow release of the silicone oil by diffusion.

The particles are preferably formed by cross-linking polymers such as polyolefins, including polyethylene, polystyrene, polydicyclopentadiene etc.; polyacrylate esters, e.g. optionally alkoxylated C_{1-10} alkyl, cycloalkyl, aryl or aralkyl esters of polyacrylic or polymethacrylic acids; polyvinyl esters e.g. polyvinyl acetate or polyvinyl laurate; polyvinyl ketones, e.g. polyvinylmethyl ketone; and polyvinyl ethers, e.g. polyvinylpropyl ether. Particular examples of suitable materials are polystyrene cross-linked with e.g. divinylbenzene and polymethacrylates cross-linked for example with ethylene glycol dimethyacrylate. The particles may be loaded with ingredients by the methods described in US 4690825 and US 5145675.

The compositions may also contain other porous particles of the same type as described above but including active ingredients instead of silicone oil, so as to provide slow release of these ingredients. This is for example useful in providing delayed release of a local anaesthetic such as benzocaine or lidocaine. The compositions may for example contain 0.5-3.5% by weight of a local anaesthetic entrapped in porous particles.

The compositions may also include further dry insoluble ingredients such as an astringent, e.g. zinc oxide, or a tissue-healing or wound-healing agent, such as a sulphated saccharide, e.g. sucrose octasulphate. The latter may be used in the form of a salt (e.g. the potassium salt) or complex with a metal, for example sucralfate (an aluminium complex), in an amount of 0.1-1%, e.g. about 0.5%, by weight.

In general the compositions may be made by preparing the aqueous and oil phases and then mixing them together and then adding the porous particles and any other dry ingredients required, using methods generally known for the manufacture of creams. A

particularly suitable method includes the steps of preparing an aqueous solution of the water soluble ingredients of the composition and mixing it with the oil phase mixture to form an emulsion, followed by the addition of a solution in a cosolvent of the active ingredient(s) which are insoluble or poorly soluble in water, again with emulsification. The dry ingredients such as the porous particles and zinc oxide are then added, and finally the dilute acid is added to adjust the pH. When a gelling agent such as PVP is included, this should be mixed into the aqueous phase before the addition of any ionic ingredients such as benzalkonium chloride.

The following example illustrates the invention.

Example 1

The following phases were prepared:

	%w/w
Water Phase	
Distilled Water	42.75
Disodium EDTA	0.10
Ganex V-220 (1)	2.00
1% Benzalkonium Chloride	10.00
Oil Phase	
Hydrolactol 70 (2)	12.00
Stearic Acid XXX	5.00
Hydrophilol Isostearique (3)	4.00
Ceteareth-20	1.00
BHT	0.10
Dow Corning 3225C (4)	0.25
APS Dimethicone Blend 200/350/1000 (5)	6.00
Active Solution Phase	
Pharmasolve (N-Methyl-2-Pyrrolidone) (6)	3.50
Hydrocortisone Acetate	0.50

Benzocaine	1.50
Dry Phase	
55% Dimethicone Microsponges (5)	7.30
40% Benzocaine Microsponges (5)	2.50
Zinc Oxide (Z-Cote HP1)	0.50
Acidulant Phase	
Distilled Water	0.65
Citric Acid	0.35
	100.00

(1) polyvinyl pyrrolidone (2-pyrrolidone-1-ethenyl polymer with 1-eicosene) from International Speciality Products of Wayne, New Jersey, USA

(2) mixture of glyceryl stearate, propylene glycol stearate, oleth 25, glyceryl isostearate, propylene glycol isostearate, cetheth 25 (Gattefosse)

(3) propylene glycol isostearate (Gattefosse)

(4) dimethicone copolyol formulation acid - a mixture containing octamethyl cyclotetrasiloxane, decamethyl cyclopentasiloxane and alkyl and alkoxy siloxanes

(5) from Advanced Polymer Systems of Redwood City, California, USA

(6) from International Speciality Products

The manufacturing procedure was as follows:

Active solution phase:

1. In a small size container, the pharmasolve was

mixed vigorously while adding slowly the amount of hydrocortisone acetate. The drug was allowed to dissolve. The mixing was continued and the amount of benzocaine was added slowly and dissolved.

Oil phase:

2. Into a suitable size kettle, all the ingredients of the oil phase were added, mixed slowly and heated to 72-76°C. After all the solids had melted, this temperature was maintained.

Water phase:

3. Into a large kettle, the amount of water was loaded, and good mixing and heating to 75-78°C initiated. While heating, disodium EDTA was added and allowed to dissolve. The mixing speed was reduced to minimum and Ganex V 220 slowly added. This was dissolved completely, avoiding air entrapment. When at 75-78°C, benzalkonium chloride solution was added. The solution was maintained at this temperature.

Emulsification:

4. When both phases were at 72-78°C, the mixing speed was increased in the large kettle containing the water phase. The oil phase was added to the water phase and mixed for 10 minutes at this temperature.

5. The mixing conditions were maintained and slow cooling to 48-52°C initiated.

6. When at 48-52°C, the active solution phase (from step 1) was added.

7. The mixing conditions were maintained and slow cooling to 36-38°C initiated.

Dry phase:

All the powders of the dry phase were blended to obtain a uniform mixture.

8. When the emulsion system is at 36-38°C, the dry blend was added and the mixing speed adjusted to obtain a uniform dispersion of powders, avoiding entrapment of air. The mixture was cooled to 30°C.

9. The acidulant phase was added to give a pH of 3.5-4.0 and mixing continued with cooling to 26-28°C.

The cream produced is an excellent vanishing cream for anorectal application. The same formulation without the hydrocortisone can be used as a burn cream.

The emulsions of the invention described above contain a silicone oil in both free form, in the oil phase, and in porous particles, to provide a longer lasting protective effect. The same principle may be used in other types of composition, such as suppositories. The invention thus also includes a suppository for the treatment of anorectal conditions which comprises a suppository base containing one or more medicaments for the treatment of the condition and a silicone oil and porous particles also containing a silicone oil and adapted for delayed release of the silicone oil, whereby in use the medicament(s) are deposited on the affected region and a protective layer of silicone oil is formed thereover.

The suppository base may, for example, be any conventional suppository base material such as glycogelatin, polyethylene glycol, fractionated palm kernel oil or, preferably, one or more natural, synthetic or semi-synthetic hard fats such as cocoa butter. A particularly preferred material is one of the range of cocoa butter products sold under the trade name Witepsol by Dynamit Nobel, Slough, England.

The medicaments may be the same as those described

above for the creams of the invention, such as local anaesthetics, anti-inflammatory steroids, antibacterials, astringents and tissue-healing or wound healing agents. The silicone oil and the porous particles may also be the same as described above.

The porous particles containing silicone oil may be dispersed throughout the base, for example by mixing them into the melted suppository base containing the medicaments before casting. Alternatively, the porous particles may be held in a cavity in the base material, for example by moulding the base containing the medicaments around pins, introducing the porous particles into the cavities and then closing the cavities with further base material.

The following is an example of a suppository of the invention.

Example 2 - Suppository

Dow Corning 360 Silicone oil (dimethasone absorbed in polystyrene-divinylbenzene porous beads, mean particle diameter 30 microns, pore volume 0.5 ml/g	10.0g
Zinc oxide	2.0g
Benzocaine	2.5g
50% Benzalkonium chloride	0.2g
Hydrocortisone acetate	0.5g
Silicone oil (Dow Corning 360)	5.0g
Witepsol S55 suppository base	72.15g
Witepsol E85 suppository base	12.65g

APS Dimethicone Blend 200/350/1000 can be used instead of the Dow Corning 360, and APS Dimethicone Microsponges (as in Example 1) can be used as the porous particles. The formulations can also include 0.5% sucralfate.

The above components apart from the porous particles containing silicone oil are blended at 55°C, cooled to 40°C and moulded around pins inserted partly

into generally cylindrical suppository moulds (50). After cooling, the pins are withdrawn, the moulds are inverted and porous particles introduced into the cavity left by each pin. The remainder of the cavity is filled with a blend of the two Witepsol bases at 40°C. After chilling, the suppositories are removed from the moulds and packaged.

Claims

1. A multiphase pharmaceutical composition for the topical treatment of a skin or anorectal condition, which includes an aqueous phase containing one or more medicaments for treating said condition, an oil phase containing a silicone oil, and porous particles also containing a silicone oil and adapted for delayed release of the silicone oil, whereby application of the composition to an affected region deposits said medicament(s) thereon and a protecting layer of silicone oil is formed over the medicament(s).

2. A composition according to claim 1 in the form of a cream.

3. A composition according to claim 1 or claim 2 which the active ingredient in the aqueous phase is a local anaesthetic, anti-inflammatory steroid, antibacterial, emollient or astringent.

4. A composition according to claim 3 which further contains a cosolvent which act as a solubiliser for an active ingredient which is insoluble or poorly soluble in water.

5. A composition according to claim 4 in which the cosolvent is N-methyl-2-pyrrolidone and the active ingredient is hydrocortisone.

6. A composition according to any preceding claim in which the aqueous phase also includes a gelling agent.

7. A composition according to any preceding claim in which the oil phase includes an emulsifier having an HLB value of 8-17 to increase its hydrophilicity and to reduce or minimise the solubility of the silicone oil in

the oil phase.

8. A composition according to any preceding claim in which the total amount of silicone oil is 7-15% by weight of the composition, with 50-70% of this in the oil phase and 30-50% in the porous particles.

9. A composition according to any preceding claim in which the oil phase further includes a silicone emulsifier.

10. A composition according to any preceding claim in which the porous particles release the silicone oil over a period of time by diffusion and also initially by the action of pressure to compress the particles.

11. A composition according to any preceding claim which further includes porous particles to provide slow release of a local anaesthetic.

12. A composition according to any preceding claim which further includes an insoluble astringent or a tissue-heating or wound-healing agent.

13. A suppository for the treatment of anorectal conditions which comprises a suppository base containing one or more medicaments for the treatment of the condition and a silicone oil and porous particles also containing a silicone oil and adapted for delayed release of the silicone oil, whereby in use the medicament(s) are deposited on the affected region and a protective layer of silicone oil is formed thereover.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/02 A61K9/10 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 90 07324 A (EDKO TRADING REPRESENTATION ;MORTON OSWALD (GB)) 12 July 1990 cited in the application see the whole document ---	1-13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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